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REVIEW

Safety aspects and side-effects of ExEm-gel and foam for uterine cavity distension and tubal patency testing



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Niek Exalto first used uterine cavity distension back in 1987, and was the first to publish on this subject. In collaboration with Mark Hans Emanuel, he invented gel instillation sonography as an improvement to saline infusion sonography, and developed ExEm[®]-gel and an applicator for this routine diagnostic procedure. ExEm[®]-foam was developed as a simplified and effective alternative for tubal patency testing in an outpatient clinic.

Abstract A state-of-the-art overview of the safety and side-effects of ExEm-gel for uterine cavity distension and ExEm-foam for tubal patency testing is presented. A literature search was carried out using PubMed, textbooks, pharmaceutical databases and reports of toxicity tests. Information on clinical use in humans and experiments in animal models was collected and grouped according to the following components: glycerol, hydroxyethyl cellulose and purified water; subjects included toxicity test, influence on sperm cells, oocytes, blastocyst development, uterine cavity distension, tubal patency testing, pain and obstetric applications. No unknown side-effects of gel or foam, or unexpected concerns about safety, were reported. More information than expected was available on the absence of effects of the components on various human tissues. Although it is difficult to prove that the search is complete, and it is possible that side-effects remain unreported, the combination of glycerol, hydroxyethyl cellulose and purified water is considered to be safe for intrauterine application and tubal patency testing, indicating an optimal risk-benefit ratio in clinical use. The safest strategy, however, is to restrict clinical examinations with gel and foam to the pre-ovulatory phase of the menstrual cycle. 

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KEYWORDS: ExEm[®]-gel, GIS, glycerol, hydroxyethyl cellulose, HyFoSy, ultrasound

Introduction

ExEm-gel (GynaecologIQ/GISKIT BV, Delft, the Netherlands) is used for gel instillation sonohysterography (GIS), and is an alternative to saline infusion sonohysterography (SIS) (Exalto et al., 2007). A prerequisite for the imaging of body cavities is the instillation of a fluid to obtain a fluid-filled cavity. The fluid has two functions: to open the cavity from its 'collapsed' state (distension), and to enhance the contrast of the image of the body cavity (Goldstein, 2010). As water easily leaks from the body cavity, it has to be replenished continuously during imaging. Gel rather than watery contrast is used for GIS, which is a simple technique offering an optimal and stable distension of the uterine cavity with minimal inconvenience for the patient (Bij de Vaate et al., 2010).

ExEm-foam (GynaecologIQ/GISKIT BV, Delft, the Netherlands) is used for hysterosalpingo-foam sonography (HyFoSy) as an alternative to hysterosalpingo-contrast sonography (HyCoSy) and hysterosalpingography (HSG) (Emanuel and Exalto, 2011; Emanuel et al., 2012; Van Schoubroeck et al., 2013). ExEm-foam (GynaecologIQ/GISKIT BV) can be created by diluting the gel in purified water. The gel is pushed rigorously through small openings in syringes or tubes. The turbulence will cause local pressure drops, resulting in air dissolving in the solution in the form of little air bubbles. These echogenic air bubbles form a foam that is stable for several minutes and, when diluted 100% with purified water, sufficient fluid passes through the patent Fallopian tubes. During the HyFoSy procedure, the Fallopian tubes will be reflected on ultrasound. The tubes will be visible for at least 1 min. If not visible, this indicates that the passage of one or both of the Fallopian tubes might be disturbed. The foam in the abdominal cavity will be processed by the body after the procedure is finished.

ExEm-gel (GynaecologIQ/GISKIT BV) contains glycerol (GLY), hydroxyethyl cellulose (HEC) and purified water. The ingredients comply with international Pharmacopeia (USP, BP, Ph.Eur). The viscosity of this gel is at least 1800 (mPa.s) and the pH varies between 5.0 and 7.5. The gel does not contain active substances such as lidocaine and chlorhexidine (Instillagel, Farco-Pharma GmbH, Köln, Germany; Urogliss, Pharmazeutische Fabrik Montavit GmbH, Absam/Tirol, Austria), chlorhexidine alone (Endosgel, Farco-Pharma GmbH, Köln, Germany) or various other chemicals (KY Jelly, Johnson and Johnson, New Brunswick, New Jersey, USA). These gels are used for urological purposes, endoscopy, anaesthetic intubation and as a vaginal lubricant. Instillagel (Farco-Pharma GmbH) was developed in the second half of the last century as an anaesthetic and antiseptic gel for use in urologic catheterization (Bressel and Staube, 1968; Doherty, 1999). Until now, few case reports of anaphylactic reactions to the chlorhexidine component have been published (TOXNET, 2013).

Toxicological effects and adverse reactions to the combination of GLY, HEC and purified water have not been reported. In this state-of-the-art overview, safety aspects and possible side-effects of ExEm-gel (GynaecologIQ/GISKIT BV) and ExEm-foam (GynaecologIQ/GISKIT BV) for clinical use in the female genital tract for routine diagnostic procedures are summarized.

Materials and methods

A literature search was conducted using PubMed, textbooks, pharmaceutical databases and reports about toxicity testing provided by the manufacturers (Farco-Pharma GmbH, Köln, Germany and GynaecologIQ / GISKIT BV, Delft, the Netherlands) of ExEm[®]-gel and ExEm[®]-foam, subsequently referred to as gel or foam.

Information on clinical use in humans and experiments in animal models were searched, and the results summarized and grouped according to the components: GLY, HEC and purified water; subjects included toxicity tests, influence on sperm cells, oocytes, blastocyst development, uterine cavity distention, tubal patency testing, pain and obstetric applications.

The MeSH terms used in the PubMed search were 'glycerol', 'hydroxyethyl cellulose' and/or 'gel instillation sonohysterography', 'hysterosalpingo-foam sonography', 'sperm cells', 'oocytes', 'endometrial cells', 'blastocysts', 'mesothelial cells', and/or 'intra-uterine', 'intra-peritoneal', 'intra-venous', 'intra-vascular', and/or 'uterine distention', 'tubal patency', 'female genital tract infections' and 'pain'. Because of the diversity of subjects and aspects, we chose targeted searches rather than a systematic review.

Results

Glycerol

Glycerol, also named glycerin, is a clear, colourless, odourless, viscous hygroscopic liquid. It is produced in the human body as a result of normal metabolism. It is an important component of cell membranes, a precursor for phospholipid and triglyceride synthesis in the liver and adipose tissue and it is metabolized in muscle and fat cells (Van Hall et al., 2002). It is used in a wide range of pharmaceutical formulations. In topical pharmaceutical formulations, it is used primarily for its humectant and emollient properties. In oral solutions and parenteral formulations, it is used mainly as a solvent and viscosity-increasing agent.

Glycerol has long been known as a laxative with an osmotic dehydrating effect. It is used in eardrops, hydrophilic cream and mixtures. Intravenous application is effective in reducing high intracranial pressure associated with stroke, cerebral infarction, Reye's syndrome and tumours of the central nervous system (Berger et al., 2005). It is also effective in treating cerebral oedema caused by cerebral trauma, as well as in bacterial meningitis (Van de Beek et al., 2012). Potential side-effects are seen only in case of high dosages: intravascular haemolysis, hypertension and arrhythmias, headache, hyperglycaemia, nausea and vomiting, nephrotoxicity and hypokalaemia (Rowe et al., 2009). It is also used for preservation of donor cornea (Chen et al., 2010).

Adverse effects are mainly caused by the dehydrating properties. Because GLY is less toxic to peritoneal cells than glucose, it is also used in peritoneal dialysis fluid. As such it is an effective osmotic agent without causing acute mesothelial damage (Smit et al., 2000) In in-vitro studies on the

effect of GLY on human peritoneal mesothelial cells, an advantageous biocompatibility profile of GLY has also been demonstrated compared with glucose (Witowski and Knapowski, 1994).

Hydroxyethyl cellulose

Hydroxyethyl cellulose is an organic chemical compound derived from cellulose. It is a non-ionic water-soluble, biocompatible and biodegradable polymer, known since the beginning of the last century (Kamel et al., 2008; Reese et al., 1950). It presents as a light tan or cream to white-coloured, odourless and tasteless hygroscopic powder. After reviewing data on clinical use in humans and data on animal experiments, including a study on intravenous injections given to dogs, HEC is considered to be non-toxic (<http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+578>).

In the treatment of constipation, HEC is known to be an effective laxative. It is also used as a substance in capsules to deliver drugs to the gastrointestinal tract and as a tablet coating as well. It is present in lubricant preparations for dry eye, contact lens care and dry mouth (Nilforoushan et al., 2005). This polymer has also been used intra-peritoneally for reducing adhesion formation (Falk et al., 1998). It is present in clysters, and has been used intravascularly for reducing local tissue reaction (Elam and Elam, 1993). In a recent large randomised controlled trial ($n = 772$), it was concluded that HEC gel is suitable as a placebo for the clinical investigation of vaginal microbicides (Richardson et al., 2013). No differences were found between gel and no gel arms in rates of genital safety events, pregnancy outcomes or sexually transmitted diseases. Also, Tien et al. (2005) concluded that vaginal HEC gel has adequate physical properties and is safe and sufficiently inactive for investigating microbicides for the prevention of sexual transmission of human immunodeficiency virus. (Tien et al., 2005).

Purified water

Purified water, already present in the gel and added in order to create foam, is a well-known specified quality of water in international Pharmacopeia. It is a clear, colourless, odourless liquid used as a solvent. Purified water is prepared from suitable potable water obtained by distillation, ion-exchange treatment, reverse osmosis or other suitable process. It has a pH of 5 to 7, and is considered to be safe in cases of intravasation, intra-abdominal application, or both.

Toxicity tests

Acute systemic toxicity of the gel was tested in the BIOSERV analytikund medizininprodukte GmbH in Rostock, Germany. Polar and apolar extraction medium prepared from the gel were injected into the tail vein of five healthy, 6–12-month-old mice. This did not induce any toxic reaction within an observation period of 72 h. Patches were applied to the skin at the back of three rabbits. No irritation was identified

according to the Primary Irritation Index. Furthermore, with the closed patch sensitization test in 10 guinea pigs, it could be demonstrated that the gel did not cause any sensitization. No toxicological or biological critical damage was caused by the gel to a monolayer of cells and no growth inhibition occurred to mouse fibroblasts (Toxicity Report, 2007).

Genotoxicity was tested in the same laboratory using the mouse lymphoma assay and the salmonella typhimurium assay. With these tests, no substances were derived that caused genotoxicity. The tested material did not cause any intracutaneous reactivity. No significant indirect haemolysis was seen, and the haemocompatibility test did not lead to a disturbance of coagulation (Genotoxicity Report, 2009).

The resorption of HEC by mesothelial cells was tested *in vitro* by applying the foam on a monolayer of human mesothelial cells and measuring concentrations in standardized occasionally performed washings of the surface. After 48 h, only small remnants of HEC could be detected (Resorption Test, 2013).

Effect on sperm cells

The spermicidal activity and cytotoxicity of HEC gel was assessed in an *in-vitro* study, using human sperm cells (Tien et al., 2005). In contrast to KY Jelly (Johnson and Johnson), no significant deleterious effects of HEC gel on sperm motility were seen, even after a 60-min incubation. It is known from another study (Shimonovitz et al., 1994) that ultrasound transmission gel in the vagina can impair sperm motility and it is, therefore, advised not to use these gels as a lubricant for the vaginal ultrasound probe during follicular follow up in the conception cycle. In cryopreservation of human sperm cells, GLY has commonly been used as a permeating cryoprotectant (Agca and Critser, 2002; Benson et al., 2012). As the gel and foam are used in infertile patients, however, it is better to test the effects of different gel solutions on sperm cell toxicity and motility within the near future than to rely on research data on the individual components of this gel.

Effect on oocytes and blastocyst development

Although the effects of gel on oocytes are as interesting as the effects on sperm cells, they are difficult to study because human oocytes are sparsely available. In a recent study about cryopreservation of antral macaque follicles and subsequent secondary follicle culture, GLY was successfully used as a cryoprotectant (Ting et al., 2013). For cryopreservation of human oocytes and follicles, however, dimethylsulphoxide is preferred above GLY because of a demonstrated better cleavage rate after fertilization (Fabbri, 2006).

Blastocyst development was not influenced by the gel, as was tested in one-cell frozen-thawed mouse embryo cultured in IVF embryo growth medium in a gassed, humidified environment for 120 h (Tucker, 2010). The GIS catheter (GynaecologIQ/GISKIT BV, Delft, the Netherlands) also proved to be non-toxic in the same mouse embryo assay test. Furthermore, no teratological effects have been reported of GLY or HEC to date (TOXNET, 2013).

Uterine cavity distension

Sonographic investigation of the uterine cavity during uterine cavity distension with gel was first described in a study on hysteroscopy (van Roessel et al., 1987). In this study, a 32% solution of dextran 70 (Hyskon, Pharmacia Laboratories, Piscataway, New Jersey, USA) was used. In another publication, Gel-KHSG (Kohlenhydrat-Sol-Gel) was used (Klug, 1991). Thereafter, SIS developed as a widespread diagnostic procedure (de Kroon et al., 2004; Goldstein, 2010). In the first report on GIS, a sterile GLY/HEC gel preparation was used also containing lidocaine and chlorhexidine (Exalto et al., 2007). The latter are ineffective and unnecessary, and only carry an unnecessary risk of cardiac complications and allergic reactions, respectively (Rijksen and Spaans, 2009). The safety profile of GIS and HyFoSy subsequently improved by omitting lidocaine and chlorhexidine in the CE-marked gel (Emanuel and Exalto, 2011; Emanuel et al., 2012; Van den Bosch et al., 2011b; Van Schoubroeck et al., 2013). After more than 60,000 procedures with the gel, no allergic reactions or infections have been reported.

Tubal patency testing

Tubal patency testing is a part of female infertility evaluation. It has been reported that sonographic patency testing has the same accuracy as HSG, without exposing women to radiation (Lim et al., 2011; Luciano et al., 2011). In an extensive literature review, it was concluded that hysterosalpingo-contrast sonography is an acceptable screening test for subfertile patients, with the potential advantage of offering comprehensive evaluation, and being methodologically simple, cost effective and time efficient (Saunders et al., 2011). A commonly used echogenic medium for HyCoSy was Echovist (Bayer Schering Pharma AG, Berlin, Germany), a suspension of soluble galactose microparticles, which is no longer available for gynaecological use. A combination of air and saline has been used as an alternative (Spalding et al., 1997). The development of HyFoSy with foam serves as an appropriate alternative for HyCoSy with Echovist (Bayer Schering Pharma AG) or saline (Emanuel and Exalto, 2011; Emanuel et al., 2012; Van Schoubroeck et al., 2013). HyFoSy with the foam also enables verification of correct placement of implants for sterilization like Essure (Bayer Healthcare AG, Leverkusen, Germany).

Pain

It is well known that intrauterine application of contrast media may cause discomfort and even pain. This may be due to dilatation of the cervix, application, filling of a balloon catheter, or both, and rapid filling of the cavity under too high pressure. Those who are experienced with HSG know that pain can be avoided by slow filling of the uterine cavity without using high pressure. The latter is more difficult in the case of SIS, which has been reported to suppress the endometrial colour signal at power Doppler evaluation of the endometrium; GIS, however, does not affect Power Doppler signal in endometrial polyps. (Van den Bosch et al., 2011a).

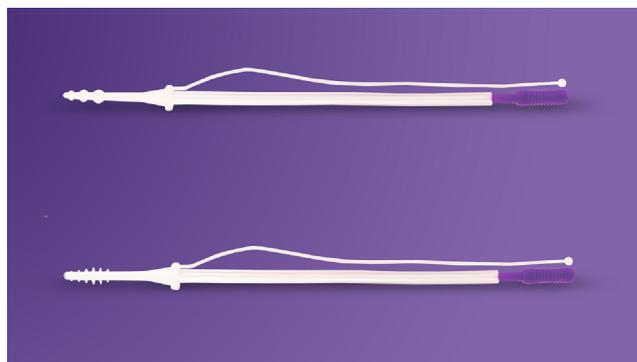


Figure 1 Catheters with cervical canules specially developed for both gel instillation sonohysterography and hysterosalpingo-foam sonography procedures.

HyCoSy with Echovist (Bayer Schering Pharma AG) and HSG were equally well tolerated in outpatient procedures for assessing tubal patency (Ayida et al., 1996). The tolerability of HyCoSy with saline was tested in a large study of 483 patients (Savelli et al., 2009). In another study, pain sensation caused by different warmth of the applied contrast agents (sterile saline and Echovist, Bayer Schering Pharma AG) was compared (Fenzl, 2012). Echovist (Bayer Schering Pharma AG) induced statistically significantly less pain compared with sterile saline of the same temperature. The most tolerable temperature for the patient is at body temperature.

Several studies have used HEC and GLY gels containing lidocaine and chlorhexidine as an intrauterine local and topical anaesthetic before various diagnostic and therapeutic procedures, without achieving an adequate reduction of pain (Zilbert, 2002). After intrauterine application of lidocaine gel for pain relief, only minimal systemic absorption of lidocaine was observed even when applied directly after endometrial ablation (Rousseau et al., 2002). A case was reported in the Netherlands of cardiac arrest occurring after using GIS with 16 ml Instillagel (Farco-Pharma GmbH) (Rijksen and Spaans, 2009). It became evident that procedure-related pain was not reduced by adding lidocaine to the gel in either GIS, office hysteroscopy, SIS or HSG (Frishman et al., 2004; Guney et al., 2007; Van den Bosch et al., 2011b). There is, as can be concluded, no rationale for using intrauterine application of lidocaine for pain reduction.

Personal experience

In over 250 cases, the special catheter with cervical canules worked perfectly and was less painful compared with the use of a hysteroscope, balloon catheter or vacuum cups (Figure 1). During placement of the canule in the cervix we start to infuse some gel or foam already to observe early leakage. There is no need for the use of a tenaculum because hardly any pressure is necessary to fill the uterine cavity and, in case of foam, the subsequent filling of the fallopian tubes is remarkably quick. Further infusion of foam is easy and passage of air bubbles can be observed. Application problems were only encountered in a few cases with obstruction of the cervical canal.

During the initial development of the HyFoSy technique, it was found that dilution of gel with purified water

compared with saline is better for producing foam and patient tolerance. In a recent randomised-controlled trial comparing HyFoSy with the traditional hysterosalpingogram, lower visual analogue scores of pain were reported during HyFoSy (Dreyer et al., 2014).

Obstetric applications

No adverse side-effects were seen in a randomized double-blind study on the efficacy of prostaglandin oestradiol during intra-cervical, intra-vaginal and extra-amniotic administration of HEC gel (Chatterjee et al., 1991). The HEC gel was used as an intra-vaginal contrast agent for sonographic examination of the cervix during pregnancy (O'Brien et al., 2003). Intermittent application of obstetric gel containing HEC and GLY into the birth canal in a randomised-controlled trial showed a significant reduction in the second stage of labour and a significant increase in perineal integrity (Schaub et al., 2008). No side-effects were observed in this study.

Discussion

The introduction of GIS has raised safety concerns (Exalto et al., 2007). A survey of the safety and side-effects of the gel 6 years after its introduction became necessary. No unknown side-effects or unexpected concerns about safety of the gel and foam were found in the literature search. On the other hand more information than expected was available about the absence of effects of the components on various human tissues.

As the gel is used for uterine cavity distention in diagnostic procedures, direct influences of the components of GLY and HEC on various tissues of the female gynaecologic tract were searched for. The osmotic dehydrating effect of GLY is the main attribute, when used for systemic and topical therapeutic and tissue protective effects, but it is also responsible for its side-effects (Van de Beek et al., 2012). The literature search found that HEC is less hygroscopic and no side-effects or inappropriate tissue reactions were found; HEC has also been used as a placebo (Richardson et al., 2013). For many years, GLY and HEC have been used for intra-vascular, intra-gastrointestinal, intra-peritoneal, intra-uterine and topical application. No allergic reactions have been described.

Animal tests for systemic and genotoxicity of the gel were carried out, with no resulting concerns about safety (Genotoxicity Report, 2009; Toxicity Report, 2007). Hydroxyethyl cellulose was resorbed by human mesothelial cells within 48 h in an in-vitro test (Resorption Test, 2013). Studies on in-vivo resorption are not yet available.

The use of foam for tubal patency testing in infertile patients highlights the necessity for looking at the influences of the components on sperm cells, oocytes and zygotes. Although HEC did not influence sperm motility, and GLY is used as a cryoprotectant in cryopreservation of human sperm cells, studies on sperm cell toxicity and motility are needed before concluding that this foam is safe for sperm cells (Benson et al., 2012; Shimonovitz et al., 1994). A comparable conclusion can be drawn for the influence on oocytes. It will, however, be

more difficult to investigate these aspects (Fabbri, 2006). It is reassuring that the gel did not influence blastocyst development, as was tested in one-cell frozen-thawed mouse embryo (Tucker, 2010). The data are overall reassuring. As safety aspects in infertility treatment are of utmost importance, however, the safest strategy is to restrict clinical examinations with gel to the pre-ovulatory phase of the menstrual cycle.

Side-effects of GIS and HyFoSy mentioned in daily practice are painful uterine contractions, vasovagal reaction, fluid loss and spotting, and do not differ from other comparable diagnostic procedures. The advantage of using gel is that it fills the uterine cavity slowly, and keeps the filling pressure low, which is the best approach to avoid pain. Sufficient evidence exists to conclude that there is no rationale for using intrauterine application of lidocaine for pain reduction.

The limitation of this overview is that it is difficult to prove that the search is complete. For practical reasons, the survey was conducted with the help of various MeSH terms and the selection of relevant publications rather than taking a systematic approach to all combinations of topics. Furthermore, direct or indirect effects may exist, and it is possible that safety aspects, side-effects, or both have not been reported.

In conclusion, data on safety and side-effects of gel and foam are reassuring and will provide support for an optimal risk-benefit ratio in clinical use. Use of HEC and GLY are considered to be safe in cases of intrauterine application, passage through the Fallopian tubes into the abdominal cavity and even in the event of the occasional occurrence of intravasation of gel or foam during the procedure. Allergic reactions and teratological effects have not been reported. It is considered prudent, however, to restrict clinical examinations with gel to the pre-ovulatory phase of the menstrual cycle.

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